REMARKS

Applicants have amended claims 39 and 46 mainly to clarify the subject matter. Support for the amendments can be found throughout the original claims and specification. No new matter has been added.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 39 and 46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

With respect to claim 39, Applicants have amended this claim to clarify that "the pharmaceutical composition is enteric-coated to inhibit degradation in the stomach" (emphasis added). Support for the amendment is found throughout the specification (e.g., page 1, lines 23-27; page 9, lines 3-7; page 11, lines 2-6). Applicants further submit that enteric coatings and methods of preparing enteric-coated capsules were well known in the art at the time this application was filed. Indeed, the terms, "enteric-coated" and "enteric coating," have been routinely used to in the art. See, e.g., five abstract printouts (enclosed herewith as **Exhibit A**) from Takenaka et al., 1980, J Pharm Sci 69:1388-92; Maharaj et al., 1984, J Pharm Sci 73:39-42; Lin and Kawashima, 1987, Pharm Res 4:70-4; Bogacz and Caldron, 1987, Am J Med 83:783-6; Gamst, 1992, Eur J Rheumatol Inflamm 12:5-8. For example, cellulose acetate phthalate was known in the art as an enteric-coating material. In light of the teachings of the specification and the knowledge in the art, one of skill in the art would readily understand the metes and bounds of the subject matter of amended claim 39.

With respect to claim 46, Applicants have amended this claim to clarify that Y is bonded to the terminal carboxy of insulin or an active fragment thereof. Support for the amendment is found throughout the specification (e.g., page 7, lines 14-15; page 8, lines 9-11; page 13, lines 1-3). Applicants submit that one skilled in the art would readily understand the metes and bounds of the subject matter of amended claim 46.

In view of the above amendments and remarks, all pending claims have satisfied the requirements under 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of the rejections are respectfully requested.

Claim rejections under 35 U.S.C. § 103

First, the Examiner rejects claim 39 under 35 U.S.C. §103(a) as allegedly being unpatentable over Ruff et al. (U.S. Pat. No. 5,446,026), alone or in view of Longenecker et al. (U.S. Pat. No. 4,994,439). Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

Ruff et al. teach the conjugation a decapeptide of calcitonin to cholic acid or chenodeoxycholic acid or deoxycholic acid at the C24 position. The conjugate was injected subcutaneously to effect analgesia. Ruff et al. make no mention of oral administration. Thus, there is no requirement to coat the conjugated peptide in order to prevent degradation by the stomach. Indeed, Ruff et al. provide no motivation to coat the conjugated peptide as the conjugated peptide of Ruff et al. was injected.

More importantly, Ruff et al. make a specific statement that the process of conjugation caused the calcitonin decapeptide to lose its anticipated natural action of enhancing calcium uptake into bone. See, e.g., "[t]his compound does not appear to enhance uptake of calcium into bone under the conditions tested in which salmon calcitonin gave a profound response" (column 3, lines 5-8). Thus, Ruff et al. teach that conjugation can in fact detrimentally affect the activity of the conjugated peptide, which in fact leads a skilled artisan away from conjugation at the C24 position.

Indeed, despite the longstanding public availability of this information as shown by filing dates of February 1993, March 1992, June 1990 and August 1989, later work on conjugation of synthetic peptides to bile salts involved the C3 position of the sterol moiety. See, for example, Kramer et al. 1994 J. Biol. Chem. 269 10621-10627 (enclosed herewith as **Exhibit B**); U.S. Pat. No. 5,668,126 (enclosed herewith as **Exhibit C**). Furthermore, Kramer et al. 1995 U.S. Pat. No. 5,462,933 (enclosed herewith as **Exhibit D**) state that "[t]he bile acids are employed in free form or in protected form" and that possible protective groups are alkyl or benzyl esters (column 8, lines 26-34), i.e., the C24 position had to be protected. Therefore, it is submitted that the precedent of Ruff et al. either provides no incentive or actually directs away those working in the field of hormone use, of peptides conjugated directly to the C24 position.

With regard to orally administered formulations, Ruff et al. fail to teach or provide motivation for making the pharmaceutical composition that is enteric-coated as recited in claim 39. Ruff et al. merely teach subcutaneous injection of liquid formulations. Such formulations are only intended to be administered by such a route and there is no teaching or suggestion to administer such a formulation orally, or to adapt the formulation to be resistant to degradation in the stomach by enteric-coating in an enteric coating. Indeed, Ruff et al. are not concerned with any possible degradation by the stomach, as the formulation is directly injected, thus by-passing the problems associated therewith. Moreover, Ruff et al. fail to teach the advantages of encapsulating the formulation in an enteric coating designed to resist degradation in the stomach, or in fact provide any evidence that the described bile salt conjugated peptides could ever be transported across the gut mucosa. In contrast, the present specification teaches an orally administrable formulation comprising a peptide conjugate to avoid the harsh environment of the digestive tract.

Applicants submit that Longenecker et al. fail to overcome the deficiencies of Ruff et al., contrary to the Examiner' assertion. Longenecker et al. claim that a mixture of a peptide/protein drug of which insulin is a named member of the group, a non-ionic detergent and either a bile salt or a fusidate can enhance absorption of the peptide/protein drug from the nasal, ocular, pulmonary, rectal or vaginal mucosa (p. 4, claim 15). This action is not a property restricted to bile salts *per se* since fusidates can apparently be substituted and with both sets of compounds the presence of a non-ionic detergent is required. In addition, many other absorption enhancing agents have been described, including, for example: (1) phosphatidylcholine (New & Kirby 1998, Hydrophobic preparations containing medium chain monglycerides, WO 98/001,690, (enclosed herewith as **Exhibit E**); (2) aromatic amides (Leone-Bay et al. 1999, Compounds and compositions for delivering active agents, U.S. Pat. No. 5,866,536, (enclosed herewith as **Exhibit F**); and (3) polyunsaturated fatty acids (Suzuki et al. 1998, Enhanced colonic and rectal absorption of insulin using a multiple emulsion containing eicsoapentaenoic acid and docosahexaenoic acid. J Pharm Sci 87, 1196-1202; enclosed herewith as **Exhibit G**).

Further, Longenecker et al. state a requirement that the bile salts, when used, must be in a concentration which exceeds the critical micellar concentration and, referring to Figure 7, a preferred value of 0.3% glycocholate was chosen which is said to be the most effective concentration. The value of 0.3% equates to 6.15 mM (0.3%, 3 g per litre, MW 488, which equals a concentration of 6.15 mM). Furthermore, at column 8, lines 36 and 37, a range of

0.1%-2.5% is given. These values contrast with the concentration of 0.2 mM used in the present studies and raise the following two issues - (1) It suggests a mechanism of action which is dependent solely upon consideration of partition coefficient and does not indicate the involvement of any active or secondary active transport; and (2) A requirement for micelle formation would not augur well for a cholate-conjugated peptide hormone since it would imply the necessity for a prohibitively high concentration of hormone: in the case of insulin this would be *ca.* 1000 I.U. ml^{-1} compared with the standard injectable dose in the UK of 100 I.U. ml^{-1}. Thus, there are disadvantages of using non-conjugated bile salts in terms of absorption across membranes and Ruff et al. do not provide any suggestion that conjugation would improve absorption across mucosal membranes.

Moreover, Longenecker et al. make no mention of absorption across intestinal membranes, whether small or large intestine (column 8, lines 16-24). The reason is explained on the basis of the capacity of the drug to irritate the digestive tract (column 4, lines 7-15). There is no clear guide to the use of bile salts in a conjugation reaction; on the contrary, there are indications of the *unsuitability* of bile salts due to the requirement to attain the micellar concentration and their capacity to irritate the gastro-intestinal tract.

In sum, Applicants submit that Ruff et al., alone or in combination with Longenecker et al. fail to teach or suggest that bile acid conjugated peptides are suitable for crossing intestinal membranes and retain peptide activity despite the harsh environment of the gut. In fact, the cited references teach away from the presently claimed invention in claim 39. At the very least, Applicants submit that claim 39 as amended is nonobvious because the cited prior art references, taken alone or in combination, fail to establish a *prima facie* case of obviousness.

Second, the Examiner rejects claims 2, 26-32, 34, 46, and 50 under 35 U.S.C. §103(a) as allegedly being unpatentable over Byun et al. (U.S. Pat. No. 6,245,753) in view of Ruff et al. and Longenecker et al. Applicants respectfully traverse this rejection.

Byun et al. describe the conjugation of heparin to a hydrophobic agent in order to promote oral administration. Heparin, as a polysaccharide (not a peptide) of variable molecular weight of 200-100,000, prevents coagulation of the blood by enhancement of the action of antithrombin III. It does not possess an active site, does not have an enzymic action, and does not activate peptide membrane-bound receptors like peptide hormones. It

was known in the art that polysaccharides are compounds that are totally different from peptides, which are characterised by primary, secondary, and tertiary structures that involve specific folding of the molecule in three dimensions.

Byun et al. disclose that the hydrophobic agent is selected from sterols (cholestanol, coprostanol, cholesterol, epicholesterol, ergosterol, ergocalciferol, and mixtures), deoxycholic acid, chenodeoxycholic acid, lithocholic acid, ursocholic acid, ursodeoxycholic acid, isoursodeoxycholic acid, lagodeoxycholic acid, glycocholic acid, taurocholic acid, glycodeoxycholic acid, glycochenodeoxycholic acid, dehydrocholic acid, hydrocholic acid, hyodeoxycholic acid, and mixtures. It is clear from this extensive and thorough list that there has been a specific omission of cholic acid as a hydrophobic agent. This is particularly remarkable given that the cholic acid is the major primary bile acid. Thus, one of ordinary skill in the art would recognize that Byun et al. is primarily concerned with the hydrophobic nature of the agents, rather than an agent being a bile salt.

Accordingly, Byun et al. merely teach conjugation of heparin, a non-peptide of non-specific form, to a hydrophobic agent which may be a sterol or one of a list of bile salts from which cholic acid was singularly omitted. In addition, Byun et al. fail to provide any motivation for one skilled in the art to attempt to conjugate a peptide hormone to the C24 residue of a bile salt (e.g., cholic acid), as recited in the present invention.

Applicants further submit that the other references cited in the Office Action fail to overcome the deficiencies of Byun et al., contrary to the Examiner's assertion. As described above, Longenecker et al. merely mention insulin as a therapeutic peptide in the general context of bile acids. Nothing in this reference would lead one of skill in the art to conjugates of bile acids and insulin or any other polypeptides. In addition, as described above, Ruff et al. actually teaches one of ordinary skill in the art away from the presently claimed invention, and from any reasonable expectation of success in doing so.

Moreover, Applicants submit that the Examiner incorrectly states that "Longenecker et al. teach the advantageous enhancement of <u>oral</u> absorption of insulin by bile acids . . ." (Office Action, page 5, lines 5-6). As described above, Longenecker et al. specifically do not refer to oral administration and in fact teach away from orally administering insulin due to irritation.

In response to the Examiner's statement that Applicants previously included polysaccharides in the list of agents, Applicants submit that polysaccharides were never

intended to be included in the claimed formulations for oral administration, but rather were relevant to a different parenteral injection aspect, which has been deleted from the original claims (see claims 21-23 of the published PCT specification). Applicants further submit that the term polysaccharide appeared in certain original claims was clearly an error as these claims always referred to amides and discussed peptide claims. Thus, contrary to the Examiner's view, the claimed invention does not cover the conjugation of polysaccharides in view of the teachings of the specification and in particular, the limitation to oral administration. In any event, the Examiner is reminded that it is the claimed subject matter that must be reviewed for patentability, not unclaimed disclosure in the specification.

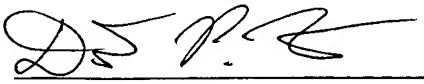
In sum, Applicants submit that claims 2, 26-32, 34, 46, and 50 are nonobvious because the cited prior art references, taken alone or in combination, fail to establish a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

For the above reasons, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited.

Although Applicants believe no fees are due with this submission, the Commissioner is hereby authorized to credit any overpayment or charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. CKFW-P01-008. Please direct any questions arising from this submission to the undersigned at (617) 951-7000.

Respectfully Submitted,



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